Special Announcement: Research Opportunities in Cutaneous Aging

(Extracted from Ongoing Program Announcements in the NIH Guide, Volume 19, Number 22, June 15, 1990.)

The National Institute of Aging and the National Institute of Arthritis Musculoskeletal and Skin Diseases wish to announce a joint program to stimulate research to define the molecular mechanisms that underlie skin photoaging and intrinsic aging. Additional aims are to establish the effectiveness and mode of actions of agents that stimulate repair of actinic damage, and to test strategies to retard or reverse age-dependent changes. The following areas of research are encouraged:

I. Molecular Mechanisms of Intrinsic Skin Aging

A. Changes in epidermal and dermal cellularity are well documented age-dependent changes in sun-protected human skin.

- Are age-dependent changes in the control of cell proliferation involved in cellular loss?
- Are changes in the expression of cellular proto-oncogenes, tumor-suppressor genes, or other cell-cycle regulatory molecules responsible for the observed age-dependent changes?
- Are senescence factors produced by aged skin cells and, if so, by what mechanisms do these senescence factors regulate cell proliferation and/or terminal differentiation of skin cells?
- Are the concentrations of endogenous growth factors altered (stimulatory and inhibitory) in aged skin?
- Are growth-factor signal-transduction pathways and cellular responses altered in aged skin cells?

B. What are the underlying molecular mechanisms responsible for loss of epidermal rete pegs and dermal papillae leading to reduced dermo-epidermal adhesion?

C. Disorganization and degeneration of the dermal matrix, including disorganization of collagen fibrillar units, degradation of elastic fibers, and loss of matrix glycosaminoglycans, is an important component of intrinsic aging in human skin.

- Are age-dependent changes in dermal fibroblast gene expression involved in dermal matrix degeneration?
- Are the observed structural changes related to altered expression of collagen genes, collagenase, elastin, elastase (serine and metalloprotease forms), and stromelysin genes?
- Are age-dependent changes in the expression of tissue-specific transcription factor genes involved in intrinsic dermal aging?

D. Disorganization and loss of the microvasculature are characteristic changes in aged skin.

- Do age-dependent changes in angiogenesis contribute to the observed loss?
- Are age-dependent changes in endothelial cell gene expression contributing factors?

E. Retinoic acid is an endogenous regulator of epidermal keratinocyte and dermal fibroblast gene expression.

- Are age-dependent changes in keratinocyte and fibroblast gene expression modulated by retinoids?
- Are intrinsic age-related changes in epidermis and/or dermis reversed by exogenous retinoids (topical retinoid treatment)?
- Are age-dependent changes in skin retinoid homeostasis (endogenous retinoid metabolite levels and retinoid metabolism) a factor in the intrinsic aging of skin?
- Are age-dependent changes in retinoic acid receptor gene expression (RAR, RARa, RARb) related to intrinsic skin aging?

II. Molecular Mechanisms of Skin Photoaging

A. Actinic damage induces keratinocyte, melanocyte, and dermal fibroblast hyperplasia in human skin.

- What are the molecular mechanisms involved in the UVR-induced changes in cell proliferation?
- Do these cellular alterations arise from acute or long-term changes in the control of cell proliferation?

B. Functionally altered fibroblasts appear to be responsible for dermal matrix degeneration in photoaged skin.

- What is the molecular basis of chronic UVR-induced solar elastosis?
- By what mechanisms does chronic UVR alter collagen I, collagen III, and elastin gene expression in the dermal fibroblast?
- Does chronic UVR alter collagenase and elastase gene expression and, if so, by what mechanisms?
- By what mechanisms does chronic UVR affect glycosaminoglycan metabolism and deposition in the dermal matrix?

C. Dermal vessels display unique damage and deterioration in photoaged skin.

- What are the mechanisms whereby chronic UVR alters endothelial cell metabolism and function?
- What role do mast cells play in vessel damage? What are the underlying mechanisms of mast cell-mediated damage?

D. Chronic UVB exposure has a pronounced and prolonged systemic immunosuppressive effect due to altered Langerhans cell function and activation of suppressor T cells.

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- What are the mechanisms responsible for the UVB-induced decreases in Langerhans cells in photoaged skin?
- What mechanisms are responsible for compromised Langerhans cells, and what are the molecular mechanisms responsible for this inappropriate immune response?

E Topical retinoids may enhance the repair of UVR-induced epidermal and dermal matrix damage in photoaged skin.

- What are the cellular, biochemical, and structural changes induced by topical retinoids in photoaged skin?
- What are the effects of retinoids on gene expression in differentiated skin cells (i.e., keratinocytes, fibroblasts, endothelial cells)?
- What are the molecular mechanisms by which retinoids regulate gene expression in skin cells?
- Is retinoid homeostasis (levels of endogenous retinoid metabolites, expression of retinoid receptors) altered in photoaged skin?

APPLICATION AND REVIEW PROCEDURES

The primary mechanisms for NIA and NIAMS support of the Biology of Aging Skin program are as follows:

Research Project Grant (R01)
Program Project Grant (P01)
First Independent Research Support and Transition Award (R29)
Fellowship Grants (F32, F33)

Applicants should use grant application form PHS 398 (revised 10/88) for R01, P01, and R29 applications and form PHS 416-1 (revised 7/88) for F32 and F33 fellowship applications. These forms are available at the applicant's institution or from the Office of Grant Inquiries, Division of Research Grants, Westwood Building, Room 449, National Institutes of Health, Bethesda, MD 20205; Telephone, (301) 496-7441.

To expedite the routing of proposals within NIH, please check "yes" in item 2 of the application face page and indicate that the proposal is in response to NIA/NIAMS: Biology of Aging Skin PA-90-16.

The completed application plus 6 copies should be sent to: Division of Research Grants, National Institutes of Health, Westwood Building, Room 240, Bethesda, MD 20892.*

Receipt dates for Research Project Grant (R01), Program Project Grant (P01), and FIRST Award (R29) applications are February 1, June 1, and October 1; Fellowship application receipt dates are January 10, May 10, and September 10.

All applications submitted in response to this announcement will be assigned according to standard referral guidelines to appropriate NIH study sections for initial scientific review and to the appropriate Institute of NIH for final review by its National Advisory Council or Board. It is anticipated that most applications will have dual Institute assignments. There are no set-aside funds for these proposals. Applications will compete for available funds based on scientific merit. Traditional NIH review criteria for scientific and technical merit will apply to all proposals submitted.

Applications from women and minority scientists are encouraged. Inclusion of minority groups and or women in study populations, where feasible and appropriate, is also encouraged by the NIH.

Investigators who may be considering submitting proposals in response to the "Biology of Aging Skin" program announcement are encouraged to discuss their research goals and the range of grant mechanisms available with NIH or NIAMS program directors prior to formal submission of research proposals. The appropriate Institute Program Directors are as follows.

Basic Mechanisms of Intrinsic Aging in Skin
Anna M. McCormick, Ph.D., Director, Genetics program, Molecular and Cell Biology Branch, Biomedical Research and Clinical Medicine Program, National Institute on Aging, Building 31, Room 5C21, Bethesda, MD 20892; Telephone, (301) 496-6402.

Basis Mechanisms of Skin Photoaging
Alan N. Moshell, M.D., Director, Skin Diseases Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, Westwood Building, Room 407A, Bethesda, MD 20205; Telephone, (301) 496-7326.

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* The mailing address given for sending applications to the Division of Research Grants or contacting program staff in the Westwood Building is the central mailing address for the National Institutes of Health. Applicants who use express mail or a courier service are advised to follow the carrier's requirements for showing a street address. The address for the Westwood Building is 5333 Westbard Avenue, Bethesda, Maryland 20816.